In the case of conflicting information, the more accurate method of estimation was used. If a range was reported (e.g. 18-20 weeks on ultrasound), the midpoint was used. In the case of multiple ultrasounds, the results of an ultrasound performed between 5 and 12 weeks of gestational age was recorded on the Pregnancy Determination Form and used for calculating the probable date of conception (PDC).

Data from the Intent-to-Treat (ITT) Evaluation Group were used to assess efficacy. Pregnancy rates were determined by using life-table analysis (estimated pregnancies per 100 woman-years of use). The endpoint of interest in the life table analysis was the six cycle cumulative probability of pregnancy. Pairwise treatment comparisons of CTR 99 and CTR 77 to Ortho-Novum 7/7/7 were performed using one-tailed logrank and generalized Wilcoxon tests. No adjustments for multiple comparisons were to be made. Pearl Indices were also calculated for the ITT group. Odds ratios and Pearl Indices were also determined for the Method Failure Group.

4.6.2 Bleeding patterns

The evaluation of bleeding patterns was based on bleeding and spotting information recorded by the subjects on daily diary cards. Bleeding was defined as any bloody discharge requiring more than one sanitary napkin or tampon per day. Spotting was any bloody discharge that did not require more than one napkin or tampon per day. For definitions of additional bleeding/spotting terms see Attachment A. Bleeding patterns were evaluated by both cycle control analysis and reference period analysis. In the cycle control analysis, the first 7 days of the first cycle were excluded and the incidence of bleeding events such as intermenstrual bleeding, breakthrough bleeding, breakthrough spotting, and absence of withdrawal bleeding were displayed. Duration of withdrawal bleeding and the number of breakthrough bleeding-spotting days were also calculated. For the reference period analysis, bleeding patterns such as amenorrhea, prolonged bleeding, and frequent and infrequent bleeding were described by a reference period (90 days) analysis using frequencies, summaries, or percentages. Each 90-day segment represented one reference period, and only subjects with a complete 90 days of information were included in any reference period. Due to the brief duration of the study, only one reference period per subject (encompassing study Days 1-90) was available for analysis. Subjects being starters or switchers, as described by cycle control analysis and reference period analysis, further categorized bleeding patterns.

4.6.3 Safety evaluation

Safety evaluation was based on the incidence of adverse experiences (AEs), discontinuations due to AEs, changes from screening to last assessment in vital signs, physical examination findings (including breast and pelvic exam and cervical Pap smear), laboratory results and pregnancy outcome. Adverse experiences and serious adverse experiences were categorized by the study period in which they occurred: pre-treatment, in-treatment, or post-treatment. Serious adverse experiences were defined as an event that was fatal or life-threatening, was permanently disabling, required an inpatient hospitalization, was a congenital anomaly, was cancer, or was caused by an overdose (whether or not it was related to the study drug). Relationship of AE to study drug was defined as:

- None-no relationship to study drug
- Unlikely-a relationship is not likely, but not impossible
- Possible-a relationship is not likely, but may exist
- Probable-a relationship has not been clearly demonstrated but is likely
- Definite-a reaction which follows a reasonable temporal sequence from administration of study drug and which is confirmed by improvement on stopping the drug and reappearance of the reaction on repeated exposure

Reviewer's comment:
It is not likely that repeated exposure ("rechallenge") would occur in the context of this study. Therefore, the designation of "definitely related" is not likely to have been made in most cases. Thus, those events which are "probably related" may be more meaningful.

4.7 All-Subjects Disposition: enrollment, withdrawals, compliance and discontinuations

8,475 subjects were enrolled in the U.S. by 132 investigators into three treatment groups (CTR 77, Ortho-Novum 7/7/7, and CTR 99). **5,552 subjects were included in the All-Subjects-Treated Group for CTR 77 and Ortho-Novum 7/7/7,** of which 35.6% were starters and 64.4% were switchers. Of these subjects, 5,344 contributed information on extent of exposure and were included in the Intent-to-Treat Evaluation Group for the assessment of efficacy.

2768 subjects were exposed to CTR 77 for a total of 14,527 cycles
1009 (36%) were Starters
1759 (64%) were Switchers
508 (18%) discontinued during the study
2260 subjects completed the study (81.6% of CTR 77 All-Subjects-Treated Group)
mean exposure was of 5.2 cycles

2784 subjects were exposed to Ortho-Novum 7/7/7 for a total of 14,758 cycles
970 (35%) were Starters
1814 (65%) were Switchers
511 (18%) discontinued during the study
2273 subjects completed the study (81.6% of Ortho-Novum 7/7/7 All-Subjects-Treated Group)
mean exposure was 5.5 cycles

Of the All Subjects Treated Groups, similar numbers (80-84%) of subjects discontinued from the 2 studies during Cycle 1-3, while 16-20% discontinued during Cycle 4-6.

Reviewer's comment:
82% of CTR 77 and ON 7/7/7 All-Subjects Treated Group completed the study. This high completion rate is related to the fact that this was only a 6-cycle trial, and may be related to the high percentage (64.4%) of Switchers in the study. Traditionally, a lower percentage of subjects complete OC trials if many of the subjects have <u>never</u> taken an OC and if the trial is of longer duration. In these two identical studies, a "starter" was any woman who had not taken an OC within two months of starting the trial. Only ~6% of the women in both arms in the two trials had <u>never</u> taken OCs prior to the study.

Dosing compliance

Subjects were to record intake of the study drug on the daily diary cards. Non-compliance was defined as missing three or more tablets consecutively or missing four or more tablets in any order, in a 28-day cycle. Compliance was similar in both treatment groups. Less than 1.3 % of the subjects in CTR 77 or Ortho-Novum 7/7/7 missed three or more tablets in any cycle.

Of the 2,656 subjects in the CTR 77 Group with evaluable diary information, approximately 7.9% to 9.5% missed one tablet, 1.9% to 3.0% missed two tablets, 0.3% to 0.8% missed three tablets, and 0.2% to 0.5% missed four or more tablets per cycle. The number of subjects for whom tablet intake information was missing ranged from 3.2% to 6.3% for any given cycle.

Reviewer's comment:
This level of non-compliance is expected in an OC study. The frequency of missed tablets was comparable among all treatment groups.

Discontinuation Reasons- see table #6 below

Table #6: Reasons for Discontinuation—Controlled Clinical Studies 092001 and 092002 (All Subjects Treated Group)

Reason for Discontinuation [a]	Starters		Switchers		Total	
	n	%	n	%	N	%
CTR 77						
Reason unknown [b]	99	9.8	55	3.1	154	5.6
Drug-related adverse experiences	66	6.5	57	3.2	123	4.4
Non-compliance	39	3.9	24	1.4	63	2.3
Personal reason	32	3.2	30	1.7	62	2.2
Non-drug-related reason	27	2.7	16	0.9	43	1.6
Pregnancy or suspicion thereof [c]						
Pretreatment	8	0.8	0	0	8	0.3
In-treatment	6	0.6	4	0.2	10	0.3
Abnormal uterine bleeding	11	1.1	12	0.7	23	0.8
Protocol violation	8	0.8	12	0.7	20	0.7
Study site closeout	1	0.1	1	0.1	2	0.1
Total discontinued CTR 77	**297**	**29.4**	**211**	**12.0**	**508**	**18.4**
Total entered	1009	100.0	1759	100.0	2768	100.0
Ortho-Novum® 7/7/7						
Reason unknown [b]	96	9.9	64	3.5	160	5.7
Drug-related adverse experiences	61	6.3	48	2.6	109	3.9
Non-compliance	38	3.9	25	1.4	63	2.3
Personal reason	31	3.2	50	2.8	81	2.9
Non-drug-related reason	18	1.9	23	1.3	41	1.5
Abnormal uterine bleeding	12	1.2	11	0.6	23	0.8
Protocol violation	12	1.2	10	0.6	22	0.8
Pregnancy or suspicion thereof [c]						
Pretreatment	0	0	0	0	0	0
In-treatment	6	0.6	4	0.2	10	0.4
Study site close out	0	0	1	0.1	2	0.1
Total discontinued ON 7/7/7	**274**	**28.2**	**237**	**13.1**	**511**	**18.4**
Total entered	970	100.0	1814	100.0	2784	100.0

[a] Reason for discontinuation as indicated on the End of Trial Case Report Form page.

[b] "Reason unknown" was specified in the CRF as "Reason unknown (e.g., lost to follow-up)."

[c] Pregnancies included 21 in-treatment pregnancies (12 in the CTR 77 Group and 9 in the Ortho-Novum® 7/7/7 Group) and 8 pre-treatment pregnancies (all in the CTR 77 Group, including 1 in the excluded Site 64/092002) for subjects in the All Subjects Treated Group. Two subjects in the CTR 77 Group (37038 and 50033) conceived in-treatment, but did not discontinue. Three subjects in the Ortho-Novum® 7/7/7 Group (37035, 37042, and 04033) conceived in-treatment, but did not discontinue.

Data for this table were obtained from Table 6 in each Clinical Study Report for 092001 and 092002 and ISE Summary Tables 3, 4, and 5 (All Subjects Treated Group) in Appendix B.

There was no significant difference in the reasons for discontinuation between CTR 77 and Ortho-Novum 7/7/7, for either starters or switchers. The discontinuation rates for menstrual AEs were the same for both groups (0.8%).

Reviewer's comment:
The most common reason for failure to complete the study was Reason Unknown. The Reason Unknown discontinuation rate of 5.6% for CTR 77 and 5.7% for Ortho-Novum 7/7/7 is acceptable. The second most common reason for discontinuation was Drug Related AE (CTR 77 was 4.4% and Ortho-Novum 7/7/7 was 3.9%). The Drug Related AE discontinuation rates were not unusually high. The Protocol Non-compliance discontinuation rates (CTR 77 was 2.3% and Ortho-Novum 7/7/7 was 2.3%) and Personal Reason rates (2.2 and 2.9%, respectively) are the third and fourth highest. There were no significant differences among treatment groups for any of the discontinuation reasons.

4.8 Contraceptive Efficacy Analysis

Contraceptive efficacy was evaluated based on the occurrence of pregnancy during the study drug administration (or "in-treatment") period.

Forty-two subjects became pregnant in the study:

- 8 pregnancies occurred prior to administration of CTR 77 tablets, including one pregnancy in the excluded Site 64/092002,
- 21 pregnancies occurred during the drug administration period (12 in the CTR 77 Group and 9 in the Ortho-Novum 7/7/7 Group), and
- 13 pregnancies (3 in the CTR 77 Group, and 10 in the Ortho-Novum 7/7/7 Group) occurred after the discontinuation of study drug.

Pregnancy Determination Forms were completed for a total of 76 subjects with suspected or confirmed pregnancies. Of these, **pregnancy was confirmed** in 42; **23 in the CTR 77 group and 19 in the Ortho-Novum 7/7/7 group**; 8 prior to start of study drug, 21 during study drug administration, and 13 after discontinuation of study drug.

Table #7-**Protocols 092001and 002: Suspected or Confirmed Pregnancies with Completed Pregnancy Determination Forms by Treatment Groups and Total**

	CTR 77	ON 7/7/7	Total
Total Pregnancies Suspected or Confirmed	33	43	76
Pregnancy Suspected/Not Confirmed	10[a]	24[b]	34
Pregnancy Confirmed (PC)	23	19	42
PC Prior to Start of Study Drug	8	0	8[c]
PC During Study Drug Administration	12	9	21
PC After Discontinuation of Study Drug	3	10	13

[a] Subject 54016 (CTR 77) discontinued due to suspicion of pregnancy but is not listed in this table because no Pregnancy Determination Form was completed since she reported that she did not take any study drug.
[b] Subject 15036 (Ortho-Novum) discontinued due to suspicion of pregnancy but is not listed in this table because no Pregnancy Determination Form was completed.
[c] Five of the 6 subjects with confirmed pre-treatment pregnancies took study drug while pregnant and hence are included in the All-Subjects-Treated group. Subject 54016 is also listed in the All-Subjects-Treated group since she returned one compact with 0 tablets, despite comments on the Drug Accountability Record, the End of Trial page, and the Post-treatment Form stating she took no study tablets.

Reviewer's comment:
As stated earlier in this review, the sponsor was aware of a problem with Dr. Fiddes (Site 64, study 002). Data from this site was not used in the sponsor's ISE. There was one pre-treatment pregnancy reported at this site, but it does not impact the Pearl Index because the subject was pregnancy prior to taking any study drug.

The sponsor was unaware, however, of any problems with Dr. Fordyce's data (Site 12, Study 002), so they did not exclude this data from their efficacy analysis. Three subjects had recorded data on dates when they were not in the clinic. Our DSI recommendation is to exclude all data from this site, which enrolled 47 CTR 77 subjects with 258 cycles of exposure and 46 ON 7/7/7 subjects with 259 cycles of exposure. There was one during-treatment pregnancy reported at this site. Later reviewer comments will analyze the efficacy (Pearl Index) with and without the data from Site 12.

4.8.1 Pregnancies conceived while on (during) study drug

For total contraceptive effectiveness, the 6-cycle cumulative life-table pregnancy rates for the Intent-to-Treat Evaluation groups were 0.0050 for the CTR 77 group, and 0.0052 for the Ortho-Novum 7/7/7 group. The results of pairwise comparisons of CTR 99 and CTR 77 versus Ortho-Novum 7/7/7 using one-tailed log-rank and generalized Wilcoxon tests show no significant difference between treatment groups.

From the sponsor's ISE, there were 21 pregnancies conceived during the treatment period [between the day of first tablet intake and the day of last tablet] for CTR 77 and Ortho-Novum 7/7/7. Twelve in-treatment pregnancies were reported for subjects in the CTR 77 Group, and nine were reported for subjects in the Ortho-Novum® 7/7/7 Group.

Table #8 below presents the pregnancy outcome for the during-treatment pregnancies. In the CTR 77 Group, five live births were reported, two spontaneous abortions, four induced abortions, and one unknown pregnancy outcome. In the Ortho-Novum® 7/7/7 Group, five live births were reported, two spontaneous abortions, and two induced abortions. There were no confirmed during-treatment pregnancies from the excluded Site 64/092002 (Dr. Fiddes).

Dates for conception or last dose of study medication are not available for all subjects who became pregnant during treatment. Subject 50033 from study 092001 was assigned an estimated date of conception of 06/01/95 based on the raw data value of 06/?/95. The date of the last dose for this subject is unknown. Subjects 23046, 37038, 37042, and 40025 from study 092001 have missing dates of conception as noted in the table.

Table #8- Combined Sponsor and MO: Pregnancies Conceived DURING the Treatment Period in Studies 001 and 002 (All Subjects Treated Group – Site 64/002 Excluded)

Study Subject/ Site # Drug	Timing of Pregnancy	Age/Parity	LMP[a] date Cycle of Conception	Investigator PDC[b]	Estimated Week of Conception after 1st pill	Pregnancy Outcome	Perfect User? MO comment
001 08048/8 **CTR 77**	During	27/G2P1	LMP 3/27/95 Cycle 3	4/13/95	10; Took 1st pill 2/5/95	Live Birth [redacted]	Yes
001 23046/23 CTR 77	During	20/G1P0	LMP 4/28/95 Cycle 3	Unknown; + hCG 5/8/95 (C4 D9)	Unknown; Took 1st pill 2/5/95; No menses C2	Spontaneous Abortion 5/12/95	No
001 34017/34 CTR 77	During	25/G4P2	LMP 4/5/95 Cycle 4	4/15/95	13; Took 1st pill 1/15/95	Live Birth [redacted]	No
001 37038/37 CTR 77	During	26/G1P1	Unknown Last pill on 3/25/95	No sono; ? pregnant btw. 6/1-22/95	Unknown; Took 1st pill 12/4/94	Unknown	Moved; lost to F/U **MO: ? POST***
001 40042/40 CTR 77	During	27/G2P2	LMP 1/23/95 Cycle 2	2/5/95	6; Took 1st pill 1/1/95	Live Birth [redacted]	Yes
001 50033/50 CTR 77	During	33/G3P0	LMP 6/24/95 ? Cycle 7 ?	Sono 7/18/95 Unknown; 6/?/95	27; Took 1st pill 11/27/94	Spontaneous Abortion	No Data missing **MO: ? POST***
002 12006/12 CTR 77 Audit OAI	During	22/G3P1	LMP 2/27/95 Cycle 4	2/18/95 **(MO PDC 3/13/95)**	14; Took 1st pill 11/13/94; stopped pills 3/5/95	[redacted]	No **MO: ? POST***
002 18007/18 CTR 77	During	21/G0P0	LMP 5/11/95 Cycle 4	4/18/95	16; Took 1st pill 1/1/95	Live Birth [redacted]	Unknown No diaries returned one pack
002 20048/20 CTR 77	During	21/G1P1	LMP10/2/95 Cycle 5	10/4/95	20; Took 1st pill 5/22/95	Live Birth [redacted]	No
002 34031/34 CTR 77	During	37/G3P1	LMP 5/1/95 Cycle 4	5/10/95	13; Took 1st pill 2/12/95	[redacted]	Yes Last pill 6/5/95
002 35035/35 CTR 77	During	29/G2P0	LMP 5/22/95 Cycle 5	6/7/95 Tetracycline 6/3-10/95	18; Took 1st pill 2/5/95	[redacted]	No
002 45015/45 CTR 77	During	21/G2P2	LMP 12/9/94 Cycle 1	12/26/94	3; Took 1st pill 12/11/94	[redacted]	No

***These 3 subjects could have possibly conceived POST (after) discontinuing study drug. See reviewer comments that follow for further discussion.**

Study Subject/ Site # Drug	Timing of Pregnancy	Age/Parity	LMP[a] date Cycle of Conception	Investigator PDC[b]	Estimated Week of Conception after 1st pill	Pregnancy Outcome	Perfect User? MO comment
001 08062/08 ON 7/7/7	During	26/G2P2	LMP 5/15/95 Cycle 4	5/29/95	14; Took 1st pill 2/26/95	Live Birth	Yes
001 14066/14 ON 7/7/7	During	28/G5P2	LMP 4/29/95 Cycle 4	5/10/95	15; Took 1st pill 1/31/95	Live Birth	No
001 37035/37 ON 7/7/7	During	26/G1P1	LMP 4/18/95 Cycle 6	5/1/95	22; Took 1st pill 12/4/94	Live Birth	Yes
001 37042/37 ON 7/7/7	During	28/G2P2	LMP 4/25/95 Unknown-est.Cycle 6	No sono; β hCG 1,402 5/22/95	Unknown; Took 1st pill 12/11/94		Yes; took Clarithromycin 4/24/95-4/30/95
001 40025/40 ON 7/7/7	During	21/G6P3	LMP 4/45/95 Unknown-est. Cycle 5	Unknown; β hCG 1,256 5/2/95 (C6)	Unknown; Took 1st pill 11/27/94	Spontaneous Ab 5/5/95	Yes
001 44010/44 ON 7/7/7	During	20/G0P0	LMP 4/10/95 Cycle 6	4/24/95 Amoxicillin prior to PDC	22; Took 1st pill 11/27/94; last pill 5/1/94	Spontaneous Ab 5/6/95	No
002 04033/04 ON 7/7/7	During	24/G0P0	LMP 6/10/95 Cycle 6	6/22/95	22; Took 1st pill 1/22/95	Live Birth	Yes
002 30037/30 ON 7/7/7	During	27/G1P0	LMP 4/19/95 Cycle 4	5/3/95	15; Took 1st pill 1/22/95		No
002 31051/31 ON 7/7/7	During	28/G2P1	LMP 5/9/95 Cycle 4	5/20/95	13; Took 1st pill 2/19/95	Live Birth	No

[a]LMP=last menstrual cycle Day 1
[b]PDC=probable date conception

***Reviewer's comments:**
The investigator PDC was to be determined by the most accurate of the predictors of pregnancy available as outlined on pg. 15 of this review. However, in three of the CTR 77 subjects (#37038, 50033, 12006), it does not appear that this was followed and the investigator's calculation of PDC is questionable. These three subjects may have conceived after taking their last active pill. Missing data makes it difficult to be certain. Subject 12006 had a reviewer's PDC occurring within 8 days of the last pill taken. This subject would normally be counted as an in-treatment pregnancy, but all data from this site (Dr. Fordyce) has been rejected by our DSI division. Therefore, this pregnancy cannot be counted in the efficacy analysis.

If these three CTR 77 subjects were not counted as during-treatment pregnancies, then there would be 9 CTR 77 and 9 ON 7/7/7 pregnancies DURING treatment. This would mean that the Pearl index would be essentially the same for both drugs. The sponsor elected, however, to use a worst-case scenario and included all three pregnancies as CTR 77 in-treatment pregnancies. If only 11 CTR 77

subjects are counted as in-treatment pregnancies, the CTR 77 Pearl index would be lowered from 1.08 to 0.98. In either analysis [12 vs. 9 or 11 CTR 77 pregnancies], the efficacy determination is acceptable.

It is interesting to note that 33% (7/21) of the during treatment pregnancies occurred at only 3 of the 132 centers in the combined studies. Study 001 site 37 had 3 pregnancies, site 8 had 2, and site 40 had 2. No site in Study 002 had > 1 pregnancy. The other 14 pregnancies were single events at 14 sites with 108 sites having no failures during treatment. There was an average of 42 subjects at each site with an even distribution on subjects taking CTR 77 and ON 7/7/7.

Perfect use was defined as no missed pills throughout the entire time in the study. Of the 12 pregnancies on CTR 77, 3 subjects had perfect use. Of the 9 pregnancies on ON 7/7/7, 5 subjects had perfect use. It is NOT clear from a careful review of the narrative summaries that any of the pregnancies were due to missed pills.

The sponsor's definition of in-treatment pregnancies included only the subjects listed in the above table. Careful analysis of the post-treatment pregnancies follows in this review and does not change the number of pregnancies [during] in-treatment.

Of the 12 pregnancies in the CTR 77 Group, six pregnancies were conceived in Cycle 4; two pregnancies were conceived in Cycle 5, and one pregnancy was conceived in each of Cycles 1, 2, 3 and 6. In the ON 7/7/7 Group, four pregnancies were conceived in Cycle 4; three pregnancies were conceived in Cycle 6; and 2 pregnancies were unknown. Twelve of the twenty-one subjects who conceived during the treatment period missed one or more doses of CTR 77 or ON 7/7/7. In the CTR 77 Group, eight of the twelve subjects (67%) missed 1 or 2 tablets: four subjects (12006, 34031, 35035, 45015) missed tablets in the same cycle in which they conceived, while one subject (20048) missed doses in the cycle before conception. The relationship of missed doses to conception cannot be determined for the remaining three subjects (18007, 23046, 50033) because of missing dosing data or conception dates. In the ON 7/7/7 Group, four of nine (44%) subjects (14066, 30037, 31051, 44010) missed one to eight doses, all in the same cycle in which they conceived. Dosing compliance is unknown for one subject (08062).

Table #9- **Treatment Cycle for 21 Pregnancies Conceived DURING Treatment Period**

Drug ⇒	CTR 77	ON 7/7/7	**Total ⇓**
Cycle 1	1	0	1
Cycle 2	1	0	1
Cycle 3	1	0	1
Cycle 4	6	4	10
Cycle 5	2	0	2
Cycle 6	1	3	4
Unknown Conception	0	2	2
TOTAL	**12**	**9**	**21**

Reviewer's comment:
The pattern of pregnancies is initially unexpected: to see 10 of the 21 pregnancies conceived during Cycle 4 and 6 during Cycles 5 + 6. We would expect to see most pregnancies occurring earlier in the study, when women are learning to correctly use OC and when the most fertile women may conceive. However, this finding probably reflects the larger than anticipated percentage of switchers (65%) and previous OC users (29%) in the combined studies; in fact, only 6% of the starters were truly first-time-ever OC users. A "starter" per protocol was anyone who had not been on an OC "in the 2 months prior to admission."

4.8.2 Pregnancies conceived prior to administration of study drug

Seven subjects in the CTR 77 Group had confirmed pre-treatment pregnancies (Table below); all subjects took study drug while pregnant and are included in the All Subjects Treated Group. No subjects in the Ortho-Novum® 7/7/7 Group had a confirmed pre-treatment pregnancy. One subject in the excluded Site 64/092002, who took CTR 77, is included in the ISS Summary Tables for this submission.

Subject 54016 from study 092001 did not take any study tablets according to the study documents. This subject is included, however, in the All Subjects Treated Group because according to the Drug Accountability Record, one compact with 0 tablets was returned. Subject 64042 from study 092002 (excluded Site 64/092002) did not take any (0) study tablets according to comments on the End of Trial page. This subject is included in the All Subjects Treated Group because according to the Drug Accountability Record, a study compact was not returned.

Table #10- Combined Sponsor and MO: Pregnancies Conceived PRIOR TO the Treatment Period in Studies 001 and 002 (All Subjects Treated Group – Site 64/002 Excluded)

Study Subject/ Site # Drug	Pregnancy Timing	Age/Parity	LMP date	Investigator PDC[b]	1st pill dose	Pregnancy Outcome	MO comment
001 09006/09 CTR 77	Pre	21/G0P0	LMP 10/4/94	10/22/94	Took 1st pill 11/6/94 Home preg test not done	[redacted]	Pt did not start pills on 1st Sunday
001 27047/27 CTR 77	Pre	30/G1P1	LMP scant 3/15/95	2/21/95	Took 1st pill 3/19/95		False negative Home preg test
001 38008/38 CTR 77	Pre	20/G0P0	LMP 12/14/94 Menses irreg 1/14-19/95	1/4/95	Took 1st pill 1/15/95		False negative Home preg test
001 54016/54 CTR 77	Pre	25/G1P1	LMP 1/15/95	No sono; No info regarding pregnancy	?? take pills- 1 pack returned empty	Unknown; Home pregnancy test ⊕	Discrepancy btw patient history and pill packs- NE[c]
002 10090/10 CTR 77	Pre	23/G2P1	LMP 3/20/95	4/4/95	Took 1st pill 4/16/95	[redacted]	Failed to perform home preg test
002 31050/31 CTR 77	Pre	21/G2P2	LMP 1/17/95	2/6/95	Took 1st and only pill 2/19/95	Live Birth	
002 52024/52 CTR 77	Pre	28/G7P6	LMP 12/14/94	1/10/95	Took 1st pill 1/15/95	[redacted]	
002 64042/64 CTR 77 **PI fraud**	Pre	24/G4P1	LMP 6/3/95	No sono; Unknown	Pills given 7/7/95	Unknown	Pt. stated she did not take study drug; no return- NE[c]

[b]PDC=probable date conception
[c]NE=non-evaluable
[e]Ab=abortion
[f]C=cycle

Reviewer's comment:
Since this was a randomized study, it is very unusual that every one of the above 8 pregnancies occurred in subjects assigned to CTR 77. After careful review of the subject narrative summaries in appendices A.3 of Volumes 51 and 71, the MO concurs with the sponsor's list of 8 pregnancies conceived prior to starting study drug. Missing or conflicting data in some cases makes it difficult to make a definitive assessment, but it is fair to conclude that seven of these eight women most probably conceived PRIOR TO starting the study drug. Therefore, they were not counted as pregnancies in any of the sponsor's calculations for efficacy (Pearl Index, Life Tables, etc.) Subjects 54016 may have conceived during Cycle 1 of CTR 77. In a worst-case scenario, she would be considered as an in-treatment pregnancy; this would make a total of 13 CTR 77 pregnancies and the Pearl index for CTR 77 would increase from 1.08 to 1.18, which is still acceptable.

4.8.3 Pregnancies conceived POST discontinuation of study drug

Thirteen post-treatment pregnancies (3 in the CTR 77 Group, 10 in the Ortho-Novum® 7/7/7 Group) were reported during the follow-up period. The date of conception for these subjects occurred following the last day of tablet intake. The estimated date of conception ranged from 15 to 35 days following the last intake of a CTR 77 tablet, and from 6 to 39 days following the last intake of an Ortho-Novum® 7/7/7 tablet (and was unknown for one subject). No post-treatment pregnancies occurred in the excluded Site 64/092002 (Dr. Fiddes). The date of conception is not known for Ortho-Novum® 7/7/7 Subject 20042 from study 092002 because of the uncertainty dating an ectopic pregnancy.

Among the thirteen post-treatment pregnancies, two subjects switched to another oral contraceptive during which pregnancy occurred, two subjects switched to a non-oral contraceptive, and two subjects confirmed no use of contraceptives because of a desire to become pregnant. In each of these situations, one subject had been on CTR 77 and one subject had received Ortho-Novum® 7/7/7 during the study. For the remaining seven post-treatment pregnancies, no information is available to confirm whether another contraceptive was used following completion of the study.

Table #11- Combined Sponsor and MO: Pregnancies conceived POST Study Treatment Period in Studies 001 and 002 (All Subjects Treated Group – Site 64/002 Excluded)

Study Subject/ Site # Drug	Timing of Pregnancy	Age/Parity	LMP date Last pill dose	Investigator PDC[b]	Number of pill cycles completed	Pregnancy Outcome	# Days after Last Dose Day[g] MO Comment
001 60015/60 **CTR 77**	Post	34/G1P1	LMP 6/14/95 stopped drug 6/17/95	7/5/95	6	[redacted]	18
002 42022/42 CTR 77	Post	24/G2P0	LMP 6/19/95 stopped drug 5/27/95	7/1/95	6	Live Birth [redacted]	35
002 66028/66 CTR 77	Post	27/G1P1	LMP 4/11/95 stopped drug 4/8/95	4/23/95	2	Live Birth [redacted]	15

Study Subject/ Site # Drug	Timing of Pregnancy	Age/Parity	LMP date Last pill dose	Investigator PDC[b]	Number of pill cycles completed	Pregnancy Outcome	# Days after Last Dose Day[g] MO Comment
001 20065/20 **ON 7/7/7**	Post	24/G1P0	LMP 4/18/95 stopped drug 4/23/95	5/5/95	2	[redacted]	12 Stopped pills due to ? of preg
001 53040/53 ON 7/7/7	Post	20/G1P1	LMP 4/1/95 stopped drug 3/25/95	4/22/95	2	[redacted]	28 Stopped pills due to honeymoon
001 56029/56 ON 7/7/7	Post	30/G2P2	LMP 5/18/95 stopped drug 5/13/95	6/1/95	4	Live Birth [redacted]	19 Stopped pills due to vacation
001 62050/62 ON 7/7/7	Post	27/G0P0	LMP 7/12/95 stopped drug 7/17/95	7/29/95	4	Live Birth [redacted]	12 Stopped pills due to move
002 20042/20 ON 7/7/7	Post-	32/G4P3	LMP10/24/95 stopped drug 10/28/95	Unknown; Sono done	6	[redacted]	Unknown # days after last dose; (Missed pills C1, 3, 4, & 5)
002 36033/36 ON 7/7/7	Post-	33/G0P0	LMP 9/19/95 stopped drug 9/23/95	9/29/95	6	Live Birth [redacted]	6 **Perfect use per MO; PDC 9/25/95**
002 41023/41 ON 7/7/7	Post	18/G1P1	LMP 8/10/95 stopped drug 8/12/95	8/23/95	6	Live Birth [redacted]	11
002 42037/42 ON 7/7/7	Post-	29/G1P0	LMP 9/14/95 stopped drug 8/5/95	9/13/95	6	[redacted]	39* ***Unknown Per MO**
002 58069/58 ON 7/7/7	Post	25/G2P2	LMP 9/18/95 stopped drug 9/6/95	10/15/95	3	Live Birth [redacted]	39
002 69022/69 ON 7/7/7	Post	27/G0P0	LMP 8/18/95 stopped drug 8/19/95	8/26/95	6	Live Birth [redacted]	7

[b]PDC=probable date conception
[c]NE=non-evaluable
[d]D=day
[e]Ab=abortion
[f]C=cycle
[g] Based on the number of days between last study dose day and the estimated date of conception; **since the last seven pills are placebo, the actual # of days from the last active dose may be up to 7 more than listed here.**

Reviewer's comments:
The distribution of the 13 post treatment pregnancies is somewhat unexpected with only 3 in the CTR 77 group and 10 in the ON 7/7/7 group. Seven subjects had completed the study (6 full cycles of treatment), while six subjects had completed from 2 to 4 cycles.

The subject narratives found in Addendum A-3 (volumes 51 and 71) were carefully reviewed for all 13 subjects. With the exception of patient 20042, each patient had a sonogram placing the date of conception after the date of last study drug administration. Patient 20042 had an ectopic pregnancy, and a sonogram done 7 weeks after the start of her LMP showed the right ectopic pregnancy (which cannot be accurately dated).

The far right column gives the sponsor's assessment of the # of days that conception occurred after the last dose of study drug. Here it is extremely important to remember that the last seven pills of each cycle were placebos, so the earliest conception (6 days with subject 36033 on ON 7/7/7) may have occurred 9-13 days after the last active OC pill (taken 9/16).

Missing or conflicting data in some cases makes it difficult to make an absolute assessment. If we use 14 days since the last active pill as a window of diagnostic uncertainty, then ON 7/7/7 subjects 36033 and 69022 would be counted as during treatment pregnancies. This would make a total of 11 Ortho-Novum 7/7/7 pregnancies and would increase the Pearl index from 0.80 to 0.97. The 3 CTR 77 subjects would remain as post-treatment pregnancies.

Pregnancies suspected but not confirmed

Pregnancy was suspected in thirty-four additional subjects (10 CTR 77 and 24 Ortho-Novum 7/7/7), but a pregnancy test was negative.

Reviewer's comment:
Pregnancy testing was to be performed in all subjects at the visits for screening, admission and Cycle 6, and for any suspicion of pregnancy during the study period. The protocol does not state any clear guidelines for pregnancy testing in subjects suspected of pregnancy at the one month Post-Treatment telephone call.

4.8.4 Pearl Index and Life Table pregnancy rate

Pearl Index

Excluding Site 64/092002, 12 of 2752 subjects in the CTR 77 Group and 9 of the 2770 subjects in the ON 7/7/7 Group (All Subjects Treated Group) became pregnant during the drug administration period. **The Pearl Index was calculated on the Intent-to-Treat Evaluation Group**, excluding Site 64/092002, which included 2643 subjects in the CTR 77 Group and 2675 subjects in the ON 7/7/7 Group with total cycles of exposure of 14,456 and 14,674, respectively. Per sponsor, the Pearl Index for All Treated Subjects was 1.08 per 100 woman years for CTR 77 and 0.80 for ON 7/7/7 (p=0.319). The pregnancy odds ratio of CTR 77 versus ON 7/7/7 was 1.351 with an upper 95% confidence interval of 2.794.

No pregnancies were conceived during treatment from Site 64/092002 (Dr. Fiddes). Because there were only 28 subjects (14 CTR 77 and 14 ON 7/7/7) with a total of 149 cycles at this site, similar results were obtained for the Pearl Index and the pregnancy odds ratio when data from Site 64/092002 were included in the calculations.

Reviewer's comment:
The above calculations by the sponsor are based on the total cycles of exposure divided by 13 pill cycles per year divided by 100 to obtain the Pearl index per 100 woman-years. The only pregnancies that are counted in their calculations are those considered to have happened while on (during) study drug. The Pearl index of 1.08 is acceptable for the CTR 77 group.

In women age 18-34 who took CTR 77, there were 11 pregnancies during 893 woman-years of exposure. The Pearl index for this age group is 1.23 per 100 woman-years.

In women age 35-50 who took CTR 77, there was one pregnancy during 219 woman-years of exposure. The Pearl index for this age group is 0.45 per 100 woman-years.

As noted in the MO analysis of the 12 during treatment pregnancies, it is possible that three of the CTR 77 subjects (# 37038, 50033, 12006) may have conceived after taking their last active pill. Missing data makes it difficult to be certain. If these three subjects were counted as pregnancies POST treatment, then there would be nine CTR 77 and nine ON 7/7/7 pregnancies DURING treatment. This would mean that the Pearl index would be essentially the same for both drugs (0.81 for CTR 77 and 0.80 for ON 7/7/7). Analyzing the post-treatment pregnancies, if we use 14 days since the last active pill as a window of diagnostic uncertainty, then ON 7/7/7 subjects 36033 and 69022 would be counted as during treatment pregnancies. This would make a total of 11 Ortho-Novum 7/7/7 pregnancies and would increase the Pearl index from 0.80 to 0.97. The 3 CTR 77 subjects would remain as post-treatment pregnancies.

In the worst case scenario, there would be 11 CTR 77 pregnancies (12 during-treatment minus 1 from Dr. Fordyce, Site 12/002) and 11 ON 7/7/7 pregnancies (9 during + 2 from the post-treatment group). In this case, the Pearl Index would be ~1.01 for both CTR 77 and ON 7/7/7, which is an acceptable Pearl Index.

Life Table Estimates

The six cycle Life-Table cumulative pregnancy rate for CTR 77 is estimated as 0.0051. For ON 7/7/7, this rate is estimated to be 0.0039. This estimate is based on in-treatment pregnancies at Cycle 6 (i.e., through 168 days). Cumulative pregnancy rates for each cycle were also provided by the sponsor. Similar estimated pregnancy rates were obtained when the data were evaluated with the excluded Site 64/092002.

These data are based on the Intent-to-Treat Evaluation Group, which included all subjects who contributed information on extent of exposure. This represented 96.3% (5,344 of 5,552) of the subjects in the All Subjects Treated Group. This is the same contribution, 96.3% (5,318 of 5,524), when Site 64/092002 is excluded.

Reviewer's comment:
It is unclear if a subject was included in the Intent-to-Treat group if she stated during a telephone contact that she took her study medication, yet failed to return diaries and pill packs. It is questionable if subjects who failed to return diaries and pill packs should be excluded from the Intent-to-Treat Evaluation.

4.8.5 Method Failure (Perfect Use) Evaluation

Of the 2,352 subjects in the CTR 77 Group who took study medication through all six cycles with perfect compliance and used no back-up methods of contraception, four pregnancies (0.2%) were conceived. Of the 2,392 subjects in the ON 7/7/7 Group with perfect compliance, eight pregnancies (0.3%) were conceived. The total exposure in the Method Failure Evaluation Group was 10,291 cycles (equivalent to 792 woman years) for CTR 77 and 10,414 cycles (equivalent to 801 woman years) for ON 7/7/7.

Reviewer's comment:
Although the data presented here by the sponsor for the "perfect use" population favors the CTR 77 product, it is the Pearl Index of the Intent-to-Treat Group that is traditionally used by the FDA. Furthermore, according to the MO analysis there were only three CTR 77 subjects (#08048, 40042, and 34031), not 4 as stated by the sponsor, and five ON 7/7/7 subjects (#08062, 37035, 37042, 40025, and 04033), not 8 as stated by the sponsor, who had "perfect use" of study drug and still conceived.

4.8.6 Bleeding patterns

The evaluation of bleeding patterns was based on bleeding and spotting information recorded by the subjects on daily diary cards. The definitions used in the analysis of bleeding parameters were identical for the two studies. Bleeding was defined as any bloody discharge requiring more than one sanitary napkin or tampon per day. Spotting was any bloody discharge that did not require more than one napkin or tampon per day. Bleeding patterns were evaluated by both cycle control analysis and reference period analysis. In the cycle control analysis, the first 7 days of the first cycle were excluded and the incidence of bleeding events such as intermenstrual bleeding (IMB), breakthrough bleeding, breakthrough spotting, early withdrawal bleeding (EWB) and absence of withdrawal bleeding (AWB) were displayed. Duration of withdrawal bleeding and the number of breakthrough bleeding-spotting days were also calculated. For the reference period analysis, bleeding patterns such as amenorrhea, prolonged bleeding, and frequent and infrequent bleeding were described by a reference period (90 days) analysis using frequencies, summaries, or percentages. Each 90-day segment represented one reference period, and only subjects with a complete 90 days of information were included in any reference period. Due to the brief duration of the study, only one reference period per subject (encompassing study Days 1-90) was available for analysis. Bleeding patterns were further categorized by subjects being starters or switchers, as described by cycle control analysis and reference period analysis.

Reviewer's comment: the usual or more common method of evaluating bleeding patterns is by cycle control.

Per Sponsor, in Protocols 092001 and 092002, CTR 77 was associated with a slightly lower incidence of breakthrough bleeding/spotting than ON 7/7/7. In the same studies, CTR 77 was associated with IMB in 11% of the total cycles, compared to 15.5% of the total cycles in the ON 7/7/7 group. This was most prominent in Cycle 1. The incidence of frequent bleeding, prolonged bleeding, infrequent bleeding, and amenorrhea was higher in the ON 7/7/7 group than in the CTR 77 group.

In Protocol 092001, regarding the two subjects who took the incorrect treatment during one cycle of the study period, the cycle they took the incorrect treatment and the next cycle were excluded from the analyses. The cycle control analysis revealed **similar mean duration of withdrawal bleeding (5.0 days for CTR 77 groups and 4.9 days for ON 7/7/7 groups).** When examining the bleeding patterns by % total cycles (see Table #12), CTR 77 had less abnormal bleeding than ON 7/7/7. However, when comparing the total number of episodes of intermenstrual bleeding in the six cycles (6969 in the CTR 77 group and 7046 in the ON 7/7/7 group), CTR 77 subjects experienced only 1.1% less episodes than Ortho-Novum subjects.

Table #12: **Bleeding Patterns in Protocols 092001 and 002**

	CTR 77 (% total cycles)	Ortho-Novum 7/7/7 (% total cycles)
Experienced Withdrawal Bleeding	**97.1**	94.8
Absence Withdrawal Bleeding	**2.9**	5.1
Early Withdrawal Bleeding	**5.7**	7.0
Intermenstrual Bleeding	**11.0**	15.5
Breakthrough Bleeding	**3.5**	4.1
Breakthrough Spotting	**7.8**	11.7

Reviewer's comment:
Because the analysis used an unusual definition for intermenstrual bleeding (IMB), it is difficult to compare bleeding results in this NDA with those in other NDAs. In the NDAs for CTR 77 and CTR

99, IMB (or breakthrough bleeding/spotting) was defined as any bleeding that occurred during the DSG interval that was neither part of early withdrawal bleeding nor continued withdrawal bleeding. In other NDAs, breakthrough bleeding/spotting was defined as any occurrence during the 21 days of active pills that was not a continuation of withdrawal bleeding. This NDA's exclusion of early withdrawal bleeding would give the appearance of better IMB bleeding rates for CTR 99 and CTR 77, than for products with IMB definitions which included early withdrawal bleeding.

The reference period analysis revealed similar bleeding patterns for the three study drugs (see Table #13) with two exceptions. Ortho-Novum 7/7/7 subjects experienced more episodes classified as frequent and infrequent bleeding than CTR 99 and CTR 77 subjects. CTR 77 subjects experienced more prolonged bleeding occurrences than CTR 99 and Ortho-Novum 7/7/7 subjects.

Table #13: **Reference Period Analysis Bleeding Patterns in Protocol 092001 and 002**

Regarding 90-day Reference Period	**CTR 77**	Ortho-Novum 7/7/7
Mean Number of Bleeding or Spotting Days*	**17.7**	17.1
Mean Number of Bleeding Days*	**11.0**	9.8
Mean Number of Spotting Days*	**6.8**	7.3
Mean Number of Bleeding-Spotting Episodes*	**3.8**	4.0
Mean Length of Bleeding-Spotting Episodes*	**4.7**	4.4
Mean Bleeding-Free Interval Length (days)*	**17.0**	16.9
Occurrence of Amenorrhea (%)	**0.05**	0.36
Occurrence of Frequent Bleeding (%)	**6.60**	10.89
Occurrence of Infrequent Bleeding (%)*	**1.27**	3.37
Occurrence of Prolonged Bleeding (%)	**3.51**	2.25

*excluded subjects with amenorrhea

Reviewer's comments:
There was no clinically significant difference in the overall bleeding patterns between the CTR 77 and ON 7/7/7 groups. Comparing starters to switchers, in both treatment groups there was a higher:

- **mean number of bleeding or spotting days**
- **mean number of bleeding-spotting episodes**
- **mean length of bleeding-spotting episodes**

Discontinuations due to menstrual problems

Menstrual problems included abnormal uterine bleeding (menorrhagia, intermenstrual bleeding, vaginal bleeding, menstrual disorder, or amenorrhea), premenstrual tension, and dysmenorrhea. Sixty-four subjects (34 in the CTR 77 Group and 30 in the ON 7/7/7 Group) discontinued from the study primarily due to menstrual problems. This includes the 46 subjects (23 in the CTR 77 Group and 23 in the ON 7/7/7 Group) for whom the discontinuation reason "abnormal uterine bleeding" was given in the Table #6 on page 17 of this review. An additional nine subjects (4 in the CTR 77 Group and 5 in the ON 7/7/7 Group) had menstrual problems that were secondary reasons for discontinuing the study. The most common menstrual problem for which subjects were discontinued was intermenstrual bleeding, reported by 37 subjects (21 in the CTR 77 Group and 16 in the ON 7/7/7 Group). The number of subjects who discontinued due to menstrual problems were similar between treatment groups (1.2% CTR 77, 1.1% ON 7/7/7).

Reviewer's comments:
There was no clinically significant difference in the overall bleeding patterns between the CTR 77 and ON 7/7/7 groups. The cycle control profile is acceptable for CTR 77.

4.9 Safety analyses

The pooled safety data evaluated CTR 77 in up to 6 consecutive cycles in 2,768 subjects (14,527 cycles of exposure) compared to 2,784 subjects (14,752 cycles of exposure) treated with Ortho-Novum 7/7/7. The populations were well balanced for all demographic characteristics in each study.

Safety evaluation was based on the incidence of adverse experiences (AEs), discontinuations due to AEs, changes from screening to last assessment in vital signs, physical examination findings (including breast and pelvic exam and cervical Pap smear), laboratory results and pregnancy outcome. Adverse experiences and serious adverse experiences (SAEs) were categorized by the study period in which they occurred: pre-treatment, in-treatment, or post-treatment. Serious adverse experiences were defined as an event that was one of the following: fatal or life-threatening, was permanently disabling, required an inpatient hospitalization, was a congenital anomaly, was cancer, or was caused by an overdose (whether or not it was related to the study drug). Relationship of AE to study drug was defined as:

- None- no relationship to study drug
- Unlikely- a relationship is not likely, but not impossible
- Possible- a relationship is not likely, but may exist
- Probable- a relationship has not been clearly demonstrated but is likely
- Definite- a reaction which follows a reasonable temporal sequence from administration of study drug and which is confirmed by improvement on stopping the drug and reappearance of the reaction on repeated exposure

Reviewer's comment:
It is not likely that a re-challenge with drug would have occurred in the context of this 6-month study. Therefore, the designation of "definitely related" is not likely to have been made in most cases. Thus, those events which are "probably related" may be more meaningful.

4.9.1 Serious Adverse Events

In the pooled data from the two studies, 1.4% (N=38; 12 starters, 26 switchers) of the CTR 77 subjects and 1.7% (N=46; 13 starters, 33 switchers) of the Ortho-Novum 7/7/7 subjects experienced an event that was classified as a "serious adverse event." This included all hospitalizations regardless of cause or reason. There was one death from asphyxiation in the study 092001: subject 37003, on Ortho-Novum 7/7/7. In study 092002, subject 14016 in the CTR 77 group died from drowning in a scuba-diving accident. Neither death was considered to be associated with study drug in the judgement of the investigator. There were no myocardial infarctions or strokes.

Five SAEs in 5 subjects were considered by the investigator to be related to study drug, as shown in the table #14 below. I t should be noted that 80 SAEs were <u>not</u> considered by the investigator to be related (i.e., none or unlikely) to study drug.

MO Table #14- **Serious Adverse Events All-Subjects-Treated Group Related to Study Drug**

Subject #	Study Drug	Event	Relatedness	During or Post Treatment
39020	**CTR 77**	**cholecystitis**	**possibly**	**during**
47011	**CTR 77**	**vascular disorder**	**possibly**	**during**
20029	**CTR 77**	**thrombophlebitis deep**	**probable**	**during**
06064	O-N 7/7/7	cholecystitis	possible	post
07045	O-N 7/7/7	Depression	definitely	post

Reviewer's comment:
Subject 39020 (Study 001): 28 year-old who was admitted to the hospital on 3/17/95, Cycle 1, Day 20 with N&V. She underwent a cholecystectomy for cholecystitis and was discharged home the next day. She continued taking CTR 77 and completed the study on 8/12/95. The investigator considered this event to be possibly related to the study drug.

Subject 47011 (Study 001): 36 year-old who was admitted to the hospital on 3/31/95 (early Cycle 6) with loss of vision in her right eye. She had experienced a similar loss of vision in April and May 1994. MRI was normal, but an arteriogram revealed a carotid artery aneurysm (vascular disorder). She underwent a surgical clipping of the aneurysm, recovered, discontinued CTR 77, and was discontinued from the study due to the event of loss of vision in her right eye. The investigator considered this event to be possibly related to the study drug.

The most significant SAE occurred in Subject 20029 (Study 002): 38 year-old non-smoker; Starter (however she had used OCs for greater than 5 years duration in the past); took CTR 77 from 3/19/95 to 4/7/95; last dose was pill # 20 during Cycle 1. She was admitted 4/8/95 with a left leg deep venous thrombosis [symptoms beginning 5-7 days previous to her admission]. The hospital discharge summary stated the DVT was confirmed by ultrasound of the lower extremities, which revealed extensive thrombosis of the left deep venous system, from the common femoral vein to the popliteal vein. [The sponsor narrative summary stated that the DVT was diagnosed by a CAT scan of the pelvis.] She was treated with heparin and Coumadin and discharged 4/13/95. She was seen for her Final Visit on 5/5/95 with her left leg noted to be slightly swollen and the Follow-up Adverse Experience Form listed "probable" as the relationship of DVT to study drug, and subject outcome as "AE still present". Venous thromboembolism (VTE) is a major safety issue for all oral contraceptives, and particularly with desogestrel-containing oral contraceptives.

Within all subjects treated in the two studies, there existed differences of opinion whether SAEs were related to study drug or not. This is not unusual. With the exception of the one CTR 77 subject with the VTE, the other pre-treatment and during-treatment SAEs were balanced between the two treatment groups. In the post-treatment phase, there were 11 serious adverse experiences reported in the ON 7/7/7 Group compared to only one in the CTR 77 treatment group (subject 23005 diagnosed with a malignant lymphoma). Subject 06064 who received ON 7/7/7 had severe cholecystitis with possible drug causality. This subject recovered without further incident. Subject 07045 had severe depression, which in the opinion of the investigator was "definitely" drug-related. This subject improved after drug was discontinued. All other serious adverse experiences in the post-treatment phase were considered to be unrelated to study drug.

4.9.2 Frequent Adverse Events

The pattern of adverse events was consistent with that seen with other third generation OCs. Overall, 67.5% of the CTR 77 subjects and 64.2% of the Ortho-Novum 7/7/7 subjects reported one or more AEs. The majority of these AEs, in all treatment groups, were considered unrelated to the use of the study drug, and relatively few were serious. Of the total population, 5.5% discontinued due to an AE. Events which most frequently led to the discontinuation of CTR 77 subjects were emotional lability (1.0%); intermenstrual bleeding (0.8%); nausea and headache (each 0.7%); depression (0.4%); nervousness, hypertension, migraine, weight increase, and dysmenorrhea (each 0.3%); and libido decreased and acne (each 0.2%). When compared to Ortho-Novum 7/7/7, there was a slightly higher incidence of discontinuation due to emotional lability and hypertension in CTR 77-treated subjects, and a slightly lower incidence of nausea, breast pain, and flatulence.

The overall incidence of in-treatment adverse experiences was comparable in the two treatment groups, (CTR 77, 68.9%; ON 7/7/7, 66.3%). Similarly, the incidence of drug-related adverse experiences was comparable in the CTR 77 treatment group (33.8%) and the group treated with ON 7/7/7 (32.4%). In both treatment groups, the system-organ class with the highest incidence of drug-related adverse experiences was reproductive, female: 482/2768 subjects (17.4%) in the CTR 77 Group and 524/2784 subjects (18.8%) in the ON 7/7/7 Group. The most frequently reported adverse events in this system-organ class were: intermenstrual bleeding (6.5% CTR 77, 8.2% ON 7/7/7), breast pain female (5.0% CTR 77, 5.7% ON 7/7/7), dysmenorrhea (5.4% CTR 77, 5.3% ON 7/7/7), moniliasis genital (4.8% CTR 77, 5.7% ON 7/7/7), vaginitis (2.1% CTR 77, 1.9% ON 7/7/7), and pelvic cramping (1.3% CTR 77, 1.0% ON 7/7/7). The remaining adverse experiences within the reproductive, female system-organ class had an incidence of ≤1% in each of the two treatment groups.

Across all system-organ classes the adverse events which were reported most commonly by CTR 77-treated subjects (i.e., by >5% of all subjects treated), and in comparison to the incidence in ON 7/7/7 subjects, were headache (15.2% CTR 77, 14.7% ON 7/7/7), upper respiratory tract infection (11.8% CTR 77, 13.2% ON 7/7/7), sinusitis (8.2% CTR 77, 8.9% ON 7/7/7), nausea (8.1% CTR 77, 7.3% ON 7/7/7), intermenstrual bleeding (6.5% CTR 77, 8.2% ON 7/7/7), dysmenorrhea (5.4% CTR 77, 5.3% ON 7/7/7), breast pain female (5.0% CTR 77, 5.7% ON 7/7/7). In general, in both the CTR 77 and the Ortho-Novum 7/7/7 Groups, the prevalence of adverse experiences appeared to decrease after the first cycle.

Sponsor Table #15: Prevalence of AEs > 5% Over All Cycles

WHO System-Organ Class WHOART Preferred Term	Incidence During Study N	 %
CTR 77 (N=2768) Number of subjects per cycle		
Headache	420	15.2
Gastrointestinal system		
Nausea	225	8.1
Reproductive, female		
Breast pain female	139	5.0
Dysmenorrhoea	150	5.4
Intermenstrual bleeding	181	6.5
Respiratory system		
Sinusitis	227	8.2
Upper respiratory tract infection	328	11.8
Ortho-Novum® 7/7/7 (N=2784) Number of subjects per cycle		
Headache	408	14.7
Gastrointestinal system		
Nausea	202	7.3
Reproductive, female		
Breast pain female	160	5.7
Dysmenorrhoea	148	5.3
Intermenstrual bleeding	228	8.2

4.9.3 Discontinuations due to AE:

See the sponsor's summary table below for the two studies.

Table #16: Adverse Experiences Leading to Discontinuation of Two or More Subjects by Preferred (WHOART) Term by Treatment Group—Controlled Clinical Studies 092001 and 092002 (All Subjects Treated Group)

System Organ Class Preferred (WHOART) Term	CTR 77 (N=2768)		Ortho-Novum® 7/7/7 (N=2784)	
	n	%	n	%
Emotional lability	27	1.0	19	0.7
Intermenstrual bleeding	22	0.8	20	0.7
Nausea	19	0.7	27	1.0
Headache	18	0.7	16	0.6
Depression	12	0.4	10	0.4
Nervousness	9	0.3	6	0.2
Hypertension	8	0.3	1	<0.1
Migraine	7	0.3	6	0.2
Weight increase	7	0.3	4	0.1
Dysmenorrhea	7	0.3	5	0.2
Libido decreased	5	0.2	3	0.1
Acne	5	0.2	4	0.1
Breast pain	4	0.1	10	0.4
Breast engorgement	1	<0.1	2	0.1
Breast enlargement	0	0	4	0.1
Fatigue	3	0.1	2	0.1
Abdominal pain	3	0.1	2	0.1
Flatulence	3	0.1	10	0.4
Female reproductive NOS	3	0.1	0	0
Menorrhagia	3	0.1	2	0.1
Pelvic cramping	3	0.1	1	<0.1
Menstrual disorder	2	0.1	3	0.1
Premenstrual tension	3	0.1	3	0.1
Ovarian cyst	1	<0.1	2	0.1
Hot flushes	2	0.1	1	<0.1
Rash	2	0.1	3	0.1
Vision abnormal	2	0.1	1	<0.1
Vomiting	1	<0.1	4	0.1
Anxiety	1	<0.1	2	0.1
Oedema generalized	0	0	4	0.1
Total number and percent of AEs leading to discontinuation	**N=159**	**5.7%**	**N=150**	**5.4%**

Reviewer's comments:
There was no clinically significant difference in the similar number of subjects who discontinued due to an AE (5.7% vs. 5.4%). Many of the AEs were single occurrences in one subject in each arm. The majority of AEs in each group were considered to be related to the study treatment (86.8% vs. 85.3%). Disorders of the female reproductive system, primarily menstrual disorders, resulted in discontinuation of study drug for 1.8% of CTR 77 and 1.6% of Ortho-Novum 7/7/7 subjects.

4.9.4 Changes in lab values

Treatment-emergent adverse events related to laboratory tests were reported during the controlled clinical studies 092001 and 092002. None were serious, and only one led to the discontinuation of the subject (1 occurrence of thrombocythemia in Ortho-Novum 7/7/7 subject 42019). In general, the incidence of adverse events related to abnormalities of hepatic enzyme levels, renal analytes, RBC or WBC indices, or coagulation indices were very low and similar between the two treatment groups. There was a slightly higher incidence of granulocytopenia and leukopenia combined in CTR 77-treated subjects (n=5, 0.2%) compared to Ortho-Novum 7/7/7 subjects (n=1, <0.1%), however none of these events were considered by the investigator to be drug-related. Furthermore, the incidence of adverse experiences related to infection (e.g., upper respiratory infection, bronchitis, pharyngitis, infection) showed no clinically significant differences between subjects who received CTR 77 and Ortho-Novum 7/7/7.

The sponsor's pooled data from studies 092001 and 092002 demonstrate that CTR 77 had no observable adverse effect on fasting serum glucose, total cholesterol, or triglycerides in over 2,000 women with up to 6 cycles of exposure. In comparison to the similar population who received Ortho-Novum 7/7/7, there were slightly higher mean increases in these parameters in the CTR 77 Group, and a slightly greater percentage of subjects with clinically significant values during treatment. Nonetheless, the mean values in the CTR 77 Group remained well within the respective normal limits at the end of these controlled clinical trials. In addition, the incidences of adverse events related to glucose and lipid metabolism were very low and similar between the two treatment groups.

Reviewer's comments:
The "normal" cholesterol range of 140-261 mg/dL cited by the Central Laboratory is certainly not desirable. Total plasma cholesterol is desirable to be less than 200 mg/dL, borderline high is 200-239 mg/dL, and high is >240 mg/dL[5]. Instead of evaluating shifts in subjects to the highest levels of cholesterol, the mean change in cholesterol levels from baseline between CTR 77 (mean change 4.0 mg/dL) and Ortho-Novum 7/7/7 (mean change 1.4 mg/dL) can be evaluated. It is the Reviewer's opinion that this difference is not clinically significant.

There was a statistically significant difference found in the mean change in triglycerides between CTR 77 (mean change 20.3 mg/dL from the mean baseline of 104.8 mg/dL) and Ortho-Novum 7/7/7 (mean change 15.6 mg/dL from mean baseline of 103.3 mg/dL). It is the Reviewer's opinion that this difference is not clinically significant.

4.9.5 Changes in vital signs, physical and gynecological exams

Although there were no apparent treatment group differences in the objective measures of blood pressure and body weight and BMI in the two trials, it should be noted that the incidences of hypertension and weight increase were slightly higher in CTR 77 subjects compared to those who received ON 7/7/7. A total of 20 (0.7%) CTR 77-treated subjects and 10 (0.4%) ON 7/7/7-treated subjects reported hypertension during treatment. This adverse event led to the discontinuation of therapy in eight (0.3%) of the CTR 77 subjects and one (<0.1%) Ortho-Novum 7/7/7 subject. An unacceptable increase in body weight was reported by 64 (2.3%) CTR 77 subjects leading to discontinuation of treatment in seven (0.3%) subjects. In comparison, 51 (1.8%) ON 7/7/7 subjects experienced weight increase, and four (0.1%) discontinued study medication. The small difference in incidence of hypertension and weight gain between the CTR 77 and the O N 7/7/7 Groups was not considered by the sponsor to be clinically significant.

In the two studies, most subjects (> 96%) in both treatment groups who completed both baseline and end of study breast examinations showed either no change or an improvement in breast nodularity, nipple contour, nipple discharge, overlying skin, and breast masses. The incidence of worsening of these breast assessments was low and occurred with similar frequency in both CTR 77 and ON 7/7/7 subjects. There was one occurrence of a breast neoplasm in a CTR 77-treated subject that led to the withdrawal of study medication. The type of neoplasm was not specified, and the subject is known to have recovered.

Post-baseline pelvic abnormalities also occurred with a similar frequency in the two treatment groups. There was one serious occurrence of a vaginal squamous cell carcinoma in an Ortho-Novum 7/7/7 subject that was first detected 2 to 2.5 months after the start of study medication. The subject was withdrawn from the study and recovered following excisional biopsy and laser ablation of the vulva and cervix. The incidence of cervical dysplasia was low and similar for the two treatment groups (0.1%). Similar percentages of subjects had abnormal Pap smears while on study medication and similar percentages were reported as adverse experiences (1.8% in CTR 77, 1.6% in ON 7/7/7). There was no clinically significant difference in physical examination or gynecological findings between starters and switchers in either treatment group.

Reviewer comment:
The reviewer agrees with the sponsor's above conclusions concerning vital signs, weight, breast and pelvic examination findings.

4.9.6 Pregnancy outcomes

The pregnancy outcome for the 12 during-treatment pregnancies in the CTR 77 Group had five live births, two spontaneous abortions, four induced abortions, and one unknown pregnancy outcome. In the Ortho-Novum 7/7/7 Group with 9 pregnancies, five live births, two spontaneous abortions, and two induced abortions were reported. The during-treatment pregnancies that resulted in live births had durations of fetal exposure to CTR 77 of 1 to 51 days in five subjects, and 11 to 22 days in five subjects exposed to Ortho-Novum 7/7/7. No congenital anomalies, stillbirths, or major newborn problems occurred.

Reviewer's comment:
This pattern of pregnancy outcome is consistent with that seen with other OCs and does not raise safety concerns regarding this product.

5.0 REVIEWER'S OVERVIEW OF EFFICACY

In an attempt to lower the cardiovascular risk associated with OCs, Organon Inc. developed [redacted] combinations, CTR 77 : [redacted] with a lower total dose of desogestrel per cycle compared to their monophasic and biphasic formulations. This submission analyzes the CTR 77 regimen which reduces both the total DSG dose and ethinyl estradiol dose by 17% compared with the monophasic Desogen® (CTR 04). The sponsor expected that this reduction would still result in acceptable efficacy, cycle control, and safety.

Since the population of subjects was demographically homogenous, no subset analyses were performed. Subjects taking a medication known to reduce OC effectiveness when concomitantly administered with an OC were excluded by protocol (see pg. 14, exclusions # 5 and 6) from the studies. Since it remains unclear whether certain antibiotics (e.g. griseofulvin, ampicillin, and tetracycline) reduce OC effectiveness when concomitantly administered with OCs, subjects taking these antibiotics were allowed into the two studies. In the pregnancy during treatment group, one ON 7/7/7 subject (44010) was taking amoxicillin 11-21 days prior to the estimated date of conception and one CTR 77 subject (35035) took tetracycline on or around the estimated conception date. Analysis of the concomitant medications administered to the ITT subjects concluded that no drug-drug interactions affected the efficacy of either CTR 77 or ON 7/7/7.

A total of 2,768 enrolled women took CTR 77. Of these, 2,260 (81.6%) completed six cycles of study drug, returned the empty Cycle 6 tablet pack, and attended a Cycle 6 visit. Data from these CTR 77 subjects and 2,688 ON 7/7/7 subjects were included in the Intent-to-Treat (ITT) Evaluation Group. The study included women up to age 50; 500 women (19.3% of the CTR 77 enrollment) were age 35-50. There were a total of 14,527 cycles of exposure in the CTR 77 ITT Group, thus the target of a total of 10,000 cycles was achieved.

Twenty-one during-treatment pregnancies were reported. Twelve of the 21 pregnancies occurred during CTR 77 treatment compared to nine pregnancies during Ortho Novum 7/7/7 treatment. The Pearl Index was calculated on the ITT group from the two studies, excluding Site 64/092002. Per the sponsor, the Pearl Index was 1.08 per 100 woman years for CTR 77 and 0.80 for ON 7/7/7 (p=0.319). The pregnancy odds ratio of CTR 77 versus ON 7/7/7 was 1.351 with an upper 95% confidence interval of 2.794. The cumulative Life Table estimates are 0.51 pregnancies per 100 woman years of use for CTR 77 and 0.39 pregnancies per 100 woman years for ON 7/7/7. When data from the excluded Site 64/092002 (Dr. Fiddes) is included in each of these calculations, similar results are obtained because no during treatment pregnancies were reported from this center which enrolled 14 subjects (71 cycles of exposure) on CTR 77 and 14 subjects (78 cycles of exposure) on ON 7/7/7.

Because the sponsor was unaware of any problems with Dr. Fordyce's data, they did not exclude the data from her Site 12, Study 002, in Albuquerque, NM. Three subjects had recorded data on dates when they were not in the clinic. Our DSI recommendation is to exclude all data from this site which enrolled 47 CTR 77 subjects with 258 cycles of exposure and 46 ON 7/7/7 subjects with 259 cycles of exposure.

> **In women age 18-34 who took CTR 77, excluding sites # 12 (Fordyce) and # 64 (Fiddes), there were 10 pregnancies during 873 woman-years of exposure. The Pearl index for this age group is 1.14 per 100 woman-years. If the two pregnancies [subjects 37038 and 50033] that may have conceived at least 14 days after the study drug was discontinued are excluded from the calculations, then the Pearl index in this age group would be 0.92 per 100 woman-years.**
>
> **In women age 35-50 who took CTR 77, excluding sites # 12 (Fordyce) and # 64 (Fiddes), there was one pregnancy [subject 34031] during 215 woman-years of exposure. The Pearl index for this age group is 0.47 per 100 woman-years.**

Worst case scenario, in All Subjects Treated who took CTR 77, including sites # 12 (Fordyce) and # 64 (Fiddes), there were 13 pregnancies [12 during treatment + subject 54016 pre-treatment] during 1117 woman-years of exposure. The Pearl index for the All Subjects Treated group is 1.17 per 100 woman-years. This is an acceptable Pearl Index.

Bleeding patterns showed no clinically significant differences between the two study groups and were very similar to patterns expected with OCs. The Sponsor reached the conclusion that in women who did not previously use OCs, cycle control during the use of CTR 77 was good. Since only 6% of the subjects were first-time-ever OC users, there were too few women in the two studies for the medical reviewer to agree with the Sponsor's conclusion. No marketing claims should be made concerning "better" cycle control with CTR 77.

The CTR 77 triphasic formulation shows adequate efficacy [overall Pearl Index of 1.08 per 100 woman-years and 6-cycle Life Table cumulative pregnancy rate of 0.0051] and cycle control for approval.

6.0 REVIEWER'S OVERVIEW OF SAFETY

The sponsor's latest safety update (January 07, 2000) was reviewed. There were no reported AE's and no subjects have taken CTR 77 since the trials were completed in February 1996.

In 1994, it was agreed between the sponsor and the reviewing division that the two clinical trials with CTR 77 could be carried out with only 6 cycles of exposure per subjects as long as each arm included 10,000 cycles of exposure. The sponsor had recently completed large clinical trials with a similar formulation, Tri-Desogen (CTR 05), using 12 and 18 months of exposure. In the All Treated Subjects group for CTR 77, there were 2,768 women who completed over 14,500 cycles of use. Although this represents a large safety database, conclusions concerning safety relate to a population of women, predominantly Caucasian (91%), who used CTR 77 for no longer than 6 months and who were mainly current OC users (64%) or past OC users ((30%). Only ~6% of the women were first-time-ever OCs users. In general, analyses of serious AEs, frequent AEs, discontinuations due to AEs, changes in lab values, changes in physical and pelvic findings show very similar results for both the triphasic CTR 77 and the comparator triphasic Ortho Novum 7/7/7. For all AEs occurring in >2% of CTR 77 subjects, there were no clinically meaningful changes in the incidence of AEs as related to smoking, age, race, or BMI, with the exception of smokers having more respiratory related AEs.

The primary safety issue is the increased risk of venous thromboembolism (VTE) in desogestrel containing OCs. The combined studies of 2,768 CTR 77 subjects reported one subject, #20029, with a deep venous thromboembolism (DVT):

> The DVT occurred in a 38 year old non-smoker who took only 20 tablets of CTR 77 during Cycle # 1. Her symptoms began on approximately pill day # 14; she was admitted to the hospital on day # 21 and treated with Heparin and Coumadin. She was discharged after 5 days in the hospital. No predisposing risk factors were reported by the sponsor.

The non-fatal VTE risk reported in the 1995 retrospective case-control WHO study [21 centers in 17 countries] was 16/100,000 in levonorgestrel containing OC users and 28-29/100,000 for desogestrel and gestodene OC users. There was one non-fatal VTEs in the 1117 woman-years of exposure to CTR 77 (14,527 cycles in CTR 77 ÷13 cycles per year = 1117 woman-years). This translates to an occurrence of non-fatal VTE of 90/100,000 woman-years, which is higher than the WHO predicted occurrence in desogestrel containing OCs. This may not be a valid comparison because the WHO study was based on a retrospective analysis. It should also be noted that compared to OCs previously reviewed by the FDA, this VTE occurrence is not statistically significant.

In studies of this size one is not likely to see a difference in safety parameters such as DVT, stroke, or MI which have continued to be a subject of concern with regard to the progestin desogestrel. In 1995, four studies found a higher risk for VTE for third generation OCs as discussed on pages 6-8 of this review. At the end of 1998, three major studies without sponsoring from the pharmaceutical industry also found a higher risk of VTE for third generation OCs, unlike three sponsored studies.[12] According to epidemiology professor JP Vandenbroucke,[13] in his February 5, 2000 letter to the BMJ editor:

"to date, of nine studies without sponsoring, one study found no difference and the other eight found relative risks between 0.8 and 4.0 (summary relative risk 2.4); four sponsored studies found relative risks between 0.8 and 1.5 (summary relative risk 1.1)."

Reviews of the increased risk of VTE with desogestrel by RMC Herings (*Lancet* '99)[14], AM Walker (*Contraception* '98)[15], the World Health Organization, the Transnational study, and the Boston Collaborative study have all **concluded that there is an increased risk (summary relative risk of 2.0 or greater) of DVT with desogestrel containing OCs. This is especially an issue with young women who were exposed to desogestrel as their initial (first-time-ever) OC use.** Furthermore, in women who are classified as thrombophilic (deficiencies of protein C, protein S, or antithrombin; or mutations in Factor V Leiden or prothrombin 20210 A), the risk of developing DVT during the first year of use, compared with longer use, was increased 11-fold (95% CI 2.1-57.3).[16]

In summary, review of the literature continues to show a safety concern of an increased risk of VTE, specifically deep vein thrombosis (DVT), in desogestrel-containing oral contraceptives compared to second generation OCs. The one case of VTE in these two trials is not statistically different from the other third generation desogestrel-containing OCs approved for marketing in the U.S. However, in this reviewer's opinion, there remains considerable concern in the literature over an increased risk of VTE events with desogestrel-containing oral contraceptives. With approval of this product, the label should clearly reflect the safety concern about an increased risk of VTE in desogestrel-containing oral contraceptives, including CTR 77.

7.0 REVIEWER'S COMMENTS ON PROPOSED LABELING

The proposed labeling is a combination of the 1994 guidance for class labeling, the August 1996 label for Desogen, the January 1998 label for Mircette, and new information. Class labeling for OCs is being revised and should apply to this OC. The sponsor was recently given notice from our Division that certain changes are needed in the Mircette label concerning the risk of VTEs and other vascular problems in OC products containing the progestin desogestrel.

[redacted]

[redacted]

The biopharmacology reviewer has made recommendations for changes in the label that would reflect several possible Drug-Drug interactions with the CYP2C9 metabolic pathway for desogestrel. These changes will be incorporated into the final label.

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[12] Vanderbroucke JP. Medical journals and the shaping of medical knowledge. *Lancet* 1998; 352: p. 2001-06.
[13] Vanderbroucke JP. Competing interests and controversy about third generation OCs. *British Journal of Medicine*; 2000; 320: p. 381.
[14] Herings RMC, Urquhart J, Leufkens HGM. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; 354: p. 127-28.
[15] Walker AM. Newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1998;57:169-81.
[16] Bloemenkamp KWM, et. al., Correspondence: Venous thromboembolism and OCs. *Lancet* 10/23/99; 354: p. 1469.

The instructions on how to take the pill are detailed and somewhat complicated. They cover the following topics:

- BEFORE you start taking your pills
- WHEN to start the FIRST pack of pills
- Important points to remember
- Day 1 start vs. Sunday start
- 21 pill pack vs. 28 pill pack
- What to do during the month
- When you finish a pack or switch your brand of pills
- What to do if you miss pills: several different scenarios are discussed
- A reminder for those on 28-day packs
- Finally, if you are still not sure what to do....

Backup methods of contraception listed in the physician and patient labels include "such as condoms, foam, or sponge." **Because there is no contraceptive sponge currently available on the U.S. market, the sponsor could consider deleting [redacted] or diaphragm" to the list of backup methods of contraception.**

The sponsor's proposed label contained no data from the large clinical trials about the design of the two identical studies, number of women enrolled, number of cycles completed, or product efficacy (Pearl Index or Life Table pregnancy rate). Furthermore, the proposed label does not contain any specific safety data about CTR 77: most common AEs; AEs causing discontinuation; serious AEs, etc. Final labeling negotiations will take these facts into consideration. It is this reviewer's opinion that such data should be included in the label in addition to the information from the guidance for class labeling for all OC products.

The final Cyclessa label should include the following clinical statement placed after Table II, (adapted from Hatcher et al.):

[redacted]

APPEARS THIS WAY
ON ORIGINAL

8.0 REVIEWER'S RECOMMENDATIONS FOR REGULATORY ACTION

Approval of CTR 77 as a triphasic combination oral contraceptive is recommended. The label should reflect the increased risk of venous thromboembolism (VTE) associated with desogestrel-containing oral contraceptives, including CTR 77 (Cyclessa). It is this reviewer's opinion that the label should also reflect some of the factual efficacy and safety data from the two large clinical trials for this drug. The instructions to patients about how and when to take the pill are somewhat complicated, but acceptable.

/S/ 3/7/00

Daniel Davis, M.D. Date
Medical Officer, HFD-580
DRUDP

/S/ 3/7/00

Shelley Slaughter, M.D., Ph.D.
Team Leader, DRUDP

cc: Daniel Davis, M.D.
Brenda Gierhart, M.D.
Shelley Slaughter, M.D.
Susan Allen, M.D.
Marianne Mann, M.D.
Jila Boal, Ph.D.
Soraya Madani, Ph.D.
Jennifer Mercier, B.S.
NDA 21-090 [redacted]
Division file
DFS: to be electronically submitted by the medical officer

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ON ORIGINAL

NDA 21-090
Cyclessa™ (desogestrel/ethinyl estradiol)

Organon, Inc.

Safety Update

Safety update is included in Medical Officer Review page 39.

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021090	Trade Name:	CYCLESSA
Supplement Number:	000	Generic Name:	DESOGETREL/ETHINYL ESTRADIOL 100UG DSG/2
Supplement Type:	N	Dosage Form:	
Regulatory Action:	AE	COMIS Indication:	PREVENTION OF PREGNANCY IN WOMAN WHO ELECT TO USE ORAL CONTRACEPTIVES AS A METHOD OF CONTRACEPTION
Action Date:	3/7/00		

Indication # 1	Oral Contraception
Label Adequacy	4
Forumulation Needed:	0
Comments (if any)	Safety and efficacy of Cyclessa (desogestrel/ethinyl estradiol) Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

Lower Range	Upper Range	Status	Date

This page was last edited on 2/25/00 12:33:00 PM

Signature /S/ — 12/20/00 Date

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21090	**Trade Name:**	[redacted]
Supplement Number:		**Generic Name:**	[redacted]
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AE	**Proposed Indication:**	Oral Contraception

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Safety and efficacy of Cyclessa (desogestrel/ethniyl estradiol) Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENNIFER MERCIER

/S/

Signature

3/6/00

Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAR 7 2000

FROM: Lisa A. Kammerman, Ph.D., Team Leader (HFD-715) 3/7/00

THROUGH: Edward Nevius, Ph.D., Division Director (HFD-715) 3-7-00

TO: NDA 21-090 (HFD-580)

SUBJECT: Deep venous thromboembolic and pulmonary embolic adverse events

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This memorandum addresses statistical issues regarding the occurrence of deep venous thromboembolic (DVT) and pulmonary embolic (PE) adverse events in NDA 21-090 and [redacted] The medical reviewers have identified one event in NDA 20-090 (Cyclessa) and two events in [redacted] This prompted one of the reviewers to compile a list of all such events reported in medical reviews of NDAs for Desogen and Mircette, which are approved third-generation oral contraceptives. Using these data, I calculated the point estimates and their exact two-sided 95% confidence intervals for:

- Number of cases (per 1000 subjects) with a DVT or PE
- Number of cases (per 100,000 women-years) with a DVT or PE

The NDAs for [redacted] nd Cyclessa have the same two studies; the other OCs had only a single study. The two studies for [redacted] and Cyclessa were combined for the assessment of DVTs and PEs. A binomial distribution was assumed for the proportion of cases with a DVT or a PE, and a Poisson process was assumed for the rates of occurrence. Women-years were calculated as (number of cycles)/13. The proportions are expressed as number of cases per 1000 subjects, and the rates are expressed as the number of cases per 100,000 women-years.

Results

To facilitate discussion, this section will use VTE (venous thromboembolic event) to refer to the occurrence of either a DVT or PE.

[redacted]

[redacted]

[redacted]

Cyclessa NDA 21-090

Cyclessa had a single VTE. Both the number of women exposed to drug and the number of women-years for Cyclessa are essentially the same as those for [redacted] The estimated proportion of Cyclessa-treated women with a VTE, therefore, and the estimated rate of VTEs are less than those estimated for [redacted] e Table).

The proportions and rates of VTEs among the Cyclessa-treated women are not unusual when compared with the results from other third-generation oral contraceptive NDAs considered in this analysis. The upper limit of the confidence interval for the proportion of women with a VTE was the smallest among the four NDAs, while the upper limit for the rate of occurrence was the second smallest.

Table. All cases of DVT and PE: # of cases per 1000 subjects and # of cases per 100,000 women-years, with the upper limits of two-sided 95% confidence intervals.

					per 1000 subjects		per 100,000 women-years	
Drug	NDA #	# Subjects Exposed to Drug	# Women-years	# Subjects with DVT or PE	# of Cases	Upper Limit of a 95% CI	# of Cases	Upper Limit of a 95% CI
Cyclessa-CTR 77	21-090	2,768	1,117	1	0.36	2.0	90	499
[redacted]		[redacted]			[redacted]			[redacted]
Desogen	20-071	1,194	879	1	0.84	4.7	113	634
Mircette	20-713	1,226	1,081	0	0.00	3.0	0	341

Conclusions

Although VTEs were present in both the Cyclessa [redacted] NDAs, there is not enough evidence to suggest these occurrences are unusual when considered in the context of the approved third-generation oral contraceptive data reviewed here.

Cc:
Original NDA 21-090
Original NDA [redacted]
HFD-580/Division File
HFD-580/BGierhart, DDavis, SSlaughter, JMercier, MMann, SAllen
HFD-715/MNg, ENevius, LKammerman